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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 121203

Application Number: 09/370,358
Filing Date: August 09, 1999
Appellant(s): SKLAR ET AL.

Mark J. Guttag
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5/19/03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

Claims 14 and 18-47 are withdrawn from consideration as not directed to the elected invention.

This appeal involves claims 1-6, 8-13, 15-17, 48, 51 and 53-57.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's grouping of the claims is acknowledged. From Appellant's arguments beginning at page 10 of the brief, it is assumed that Appellant intends that claims 1, 6, 9-13, 15-17 should be grouped together and separately from claims 54-57.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5583010	Baumbach	12/1996
5639603	Dower	6/1997

Robeva, A.S., et al., Molecular Characterization of Recombinant Human Adenosine Receptors, Drug Development Research 39(243-252)1996

Robeva, A.S., et al., Double Tagging Recombinant A1 and A2A-Adenosine Receptors with Hexahistidine and the FLAG Epitope, Biochemical Pharmacology 51(545-555)1996.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 6, 9-13, 15-17, 48, 50, 51, and 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5583010 in view of U.S. Patent No: 5639603.

U.S. Patent No: 5583010 disclose methods for non-cellular display (e.g. purified recombinant receptor, col 19, L65) of a 7TM receptor (Growth hormone releasing hormone receptor GHRH-R) comprising incorporating an attachment scheme to the receptor (col 20, L1-

3), solubilizing the receptor by lysing cell membranes containing the receptor (e.g. col 10, l24-29), presenting the receptor with in conjunction with a solid support (col 19 L65-col 20 L12), presenting one ligand to bind to the receptor, wherein said ligand is known to bind to the receptor (e.g. GHRH), and combining receptor and ligand to accomplish binding (col 19 L65-col 20 L12). Also, U.S. Patent No: 558310 state that "these assays can be linked to a reporter such as an antibody, biological chemical..., which will express a radioactive, chemical, calorimetric or luminescent signal" see col 20 L4-7; thus one of ordinary skill in the art would understand from this teaching, and particularly from the term "luminescent signal", that it is meant the receptor ligand pairs can be sorted by fluorescence.

The claims also stipulate that the method of sorting be flow cytometry and that the solid support be bead substrates appropriate for flow cytometry. Additionally claims 54-57 require that the tag be an epitope tag, e.g. either an N or C-terminal, or internal epitope. One of ordinary skill in the art appreciates that at col 20, first paragraph, U.S. Patent No: 5583010 refers to such attachment means in the statement "Solid phase assays can involve receptor attached to a solid support either chemically or immunologically..."

Although U.S. Patent No: 5583010 appears to be silent with regard to flow cytometry, flow cytometry is a well known method of sorting fluorescently labelled receptor-ligand pairs. U.S. Patent No: 5639603 teaches the general applicability of flow cytometry to the sorting of isolated solubilized receptors and their bound ligands, wherein the solid supports are beads appropriate for flow cytometry and for library screening (see col 31, L40-54). Further, Patent No: 5639603 teaches that the receptor (e.g. col 31, L58) or the ligand (col 36, L35-38) be labelled with a fluorescently labelled marker.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success to use beads as the solid support and to separate the receptor-ligand pairs by flow cytometry as taught by U.S. Patent No: 5639603, when practicing the assay of soluble receptors attached to solid supports as taught by U.S. Patent No: 5583010. The motivation to do so was provided by U.S. Patent No: 5639603 wherein it is taught that "by adopting cell sized solid supports or beads, one can use flow cytometry for high sensitivity receptor binding analysis and facile bead manipulation" (see col 31, L47-54).

Claims 2, 3-5 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5583010, in view of U.S. Patent No: 5639603 as applied to claims 1, 6, 9-13, 15-17, 48, 50, 51, and 53-57 above, and in further view of Robeva, AS *et al., Drug Development Research* 39(243-252)1996.

Claims 2, 3-5 and 8 stipulate that the tether or attachment means be a C-histidine or an N-histidine tag and that the bead be a Ni-silica bead and that the step of solubilizing the receptor comprise lying the cell membranes. The use of histidine tags in the receptor art is old. Further, is well known that Ni-silica beads are used with histidine tags. Robeva et al. disclose a method of displaying a 7TM receptor (Adenosine receptor) comprising incorporating an attachment scheme (e.g. hexahistidine tag) into the Adenosine receptor (GPCR construct), solubilizing the receptor by lysing membranes comprising the receptor (page 245) , presenting the receptor on a solid support (e.g. Ni-NTA agarose, page 245), wherein said method further comprises the step of combining the receptor and a ligand to accomplish binding (see page 244, col 2).

Additionally, whether to use the tag at The N or C-terminal is an obvious matter of routine optimization of operating parameters. Further, Rebeva teach that the step of incorporating an attachment scheme comprises incorporating the tag (coding sequence) into an oligonucleotide: see page 244, MATERIALS AND METHODS, wherein the method of subcloning the Adenosine receptor is referenced in Robeva et al., 1996, Biochem. Pharm. 51:545-555, wherein it is indicated that the tags are incorporated using a 30 base pair oligonucleotide, see Robeva et al., 1996, Biochem. Pharm, page 554.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to, with reasonable expectation of success to use histidine tags as taught by Robeva, as the attachment means for the assay disclosed by U.S. Patent No: 5583010 and modified according to the teachings of U.S. Patent No: 5639603, as discussed above. The motivation to do so was provided by Robeva, AS et al., Drug Development Research wherein it is stated that their method should be useful for other proteins and for a variety of methods including reconstitution assays (see page 554), reconstitution assays being required for solubilization of the receptor, as per the instant invention.

(11) Response to Argument

(1) Whether the rejection under 35 U.S.C. j 103(a) of claims 1, 6, 9-13, 15-17, 48, 50, 51 and 53-57 as being unpatentable over U.S. Patent No. 5,583,010 (Baumbach) in view of U.S. Patent No. 5,639,603 (Dower) should be withdrawn as improper and claims 1, 6, 9-13, 15-17, 48, 50, 51 and 53-57 allowed, because the combination of Dower with Baumbach is improper.

At page 6 of the Brief, Appellant argues that rejection of claims 1, 6, 9-13, 15-17, 48, 50, 51, and 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5583010 (Baumbach) in view of U.S. Patent No: 5639603 (Dower) is improper because the asserted motivation is provided by Dower and not Baumbach. This argument has been fully considered but not deemed persuasive. The examiner can find no reason why this should be improper and nor has Appellant provided any reference for the authority of their assertions. Moreover, MPEP 2443.01 does not indicate that the motivation must be found in a particular reference. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313.

(2) Whether the rejection under 35 U.S.C. j 103(a) of claims 1, 6, 9-13, 15-17, 48, 50, 51 and 53-57 as being unpatentable over U.S. Patent No. 5,583,010 (Baumbach) in view of U.S. Patent No. 5,639,603 (Dower) should be withdrawn as improper and claims 1, 6, 9-13, 15-17, 48, 50, 51 and 53-57 allowed, because the combination of Dower with Baumbach fails to teach or suggest the methods of claims 1, 6, 9-13, 15-17, 48, 50, 51 and 53-57.

Appellant argues that no grounds have been provided as to why a person of ordinary skill in the art would be motivated to combine Dower and Baumbach. This argument has been fully considered but not deemed persuasive. The motivation to do so was provided by Dower wherein it is taught that "by adopting cell sized solid supports or beads, one can use flow cytometry for high sensitivity receptor binding analysis and facile bead manipulation" (see col 31, L47-54). Baumbach teach the desirability to perform ligand binding assays using a bound receptor and ligand, e.g. col 19 L65-col 20 L12. Dower teach a refined method for performing such assays, e.g. flow cytometry, therefore it would be obvious for one of ordinary skill in the art practicing the general teachings of Baumbach regarding assay systems to turn to the more refined method of Dower.

Appellant argues that Baumbach and Dower fail to teach or suggest analyzing with a flow cytometer in real time as recited in claim 1. This argument has been fully considered but not deemed persuasive. One of ordinary skill in the art appreciates that, even with the wash step (exclusion of which is not a positive claim limitation), Dower teaches analyzing with flow cytometery in real time, i.e. the disassociation of the ligand and the receptor is happening as they are being analyzed in the flow cytometer. Appellant has done essentially the same thing.

Appellant argues that the methodology employed by Dower is differs in several respects from claim 1; namely that Dower solubilizes and binds a ligand library to a bead whereas claim 1 requires that the receptor be attached to a bead via a tether. This argument has been fully considered but not deemed persuasive. First, Appellant is reminded that the rejection is under 35 USC 103, therefore no single prior art reference need teach each and every limitation; otherwise

the rejection would be under 35 USC 102. Secondly, Dower reviews many particular ways of performing the assay e.g. with the ligand immobilized, as referred to by Appellant, or with the receptor immobilized, see col 36, L28-43. All of these configuration would be obvious to one of ordinary skill in the art depending on the particular application required.

Appellant argues that Dower requires a wash step. This argument has been fully considered but not deemed persuasive. The instant claims do not exclude a wash step. And, as set forth above, there is no indication that a wash step would negate analysis in real-time as Appellant appears to suggest although it does not appear that Appellant actually makes the assertion. Appellant further argues that the only example of a flow cytometry process not requiring a wash step that is mentioned by the examiner is that of Appellant's invention and that it is improper to use Appellant's teachings against them. This argument has been fully considered but not deemed persuasive. The basis of the rejection and subsequent arguments has nothing to do with a wash step. The claims require nothing regarding a wash step. Appellant's arguments are not commensurate in scope with what is being claimed. The rejection is also not based on Appellant's disclosure. Importantly, Appellant's do not challenge the examiner's assertion that "If one were using the method of Dower to analyze the interaction between a receptor and it's known ligand, as [Applicant] points out, then a wash step would *obviously* not be required" [emphasis added], see page 9 of the brief. Thus, the examiner maintains that the ability of a flow cytometric measurement to discriminate free and bound ligand with-out a wash step was widely appreciated at the time of filing of the instant Application. Appellant's have not asserted that the elimination of a wash step would not be obvious to one of ordinary skill in the art when analyzing the interaction between a receptor and it's known ligand. Again, Appellant

has not argued the validity of the examiner's position, only that the examiner has not provided a specific reference for a concept that the examiner believes was widely appreciated in the art. For the purposes of the instant claims, however, any discussion of a wash step appears to be moot given the comprising (open) language of the claimed invention.

At pages 10-12 of the brief, Appellant argues that claims 54-57 are patentable because the examiner has cited no reference that teaches or suggests the step of incorporating an attachment tether to a receptor comprising incorporating at least one epitope tag, e.g. either at the N-terminal (claim 55), the C-terminal (claim 56), or at an internal site (claim 57) of the receptor. This argument has been fully considered but not deemed persuasive. . It should be noted that the at page 4, first full paragraph, of the Final rejection, the examiner incorrectly referred to U.S. Patent No: 5639603 as teaching "Solid phase assays can involve receptors attached to a solid support either chemically or immunologically", rather it is U.S. Patent No: 5583010 that provides this teaching, see col 20, first paragraph.

At page 10, third paragraph of the brief, Appellant misquotes the Final action stating that "claims 54-57 require that the tag be an epitope tag, e.g. either an N or C-terminal epitope…". This is not correct. The Final Office action states that "claims 54-57 require that the tag be an epitope tag, e.g. either an N or C-terminal, *or internal epitope*" [emphasis added] see page 4, second full paragraph, of the Final Office action. The examiner can think of no place to put an epitope tag other than at the N-terminal, the C-terminal or at an internal site. Thus claims 54-57 provide for the placement of the tag at any place on the protein. This is identical in scope to the teaching in the prior art patent that "solid phase assays can involve receptors attached to a solid support either chemically or immunologically" see U.S. Patent No: 5583010, col 20, first

paragraph. However, at pages 10-12 of the brief Appellant argues that the examiner has cited no prior art indicating that one of ordinary skill in the art would understand the cited paragraph to teach or suggest the features of incorporating an attachment tether comprising an epitope tag at either the N or C terminal or an internal site, as required individually by claims 54-57. No prior art was cited as evidence of the examiner's interpretation of the teaching of the 5583010 patent because the examiner can think of no way to attach something "immunologically" without an epitope, and nor can the examiner think of a way of placing an epitope other than at the N or C terminal or an internal site. Importantly, Appellant does not assert that the examiner's assertions are incorrect, merely that the examiner has failed to provide a reference for a concept that the examiner believes is well established in the art.

With respect to claim 48 and dependent claims 51 and 53, beginning on page 12, Appellant essentially repeats arguments made previously regarding claim 1. These arguments have been thoroughly addressed above regarding claim 1 and are not persuasive.

3) Whether the rejection under 35 U.S.C. j 103(a) of claims 2-5 and 8 as being unpatentable over U.S. Patent No. 5,583,010 (Baumbach) in view of U.S. Patent No. 5,639,603 (Dower), and further in view of Robeva should be withdrawn as improper and claims 2-5 and 8 allowed, because the combination of Robeva with Dower and Baumbach is improper.

Appellant essentially repeats arguments regarding claim 1 which have been discussed above.

(4) Whether the rejection under 35 U.S.C. j 103(a) of claims 2-5 and 8 as being unpatentable over U.S. Patent No. 5,583,010 (Baumbach) in view of U.S. Patent No. 5,639,603 (Dower), and further in view of Robeva should be withdrawn as improper and claims 2-5 and 8 allowed, because the combination of Robeva with Dower and Baumbach fails to teach or suggest the methods of claims 2-5 and 8.

Appellant essentially repeats arguments regarding the combination of Baumbach and Dower as discussed previously regarding claim 1. These arguments have been addressed above.

(5) Claims 1-6, 8-13, 15-7, 48, 51, and 53-57 have been rejected upon facts within the personal knowledge of the Examiner, and Applicants hereby request under 37 C.F.R. j 1.104(d)(2) that the Examiner provide an affidavit supporting the Examiner's assertions used as a basis for the rejections of these claims.

Applicant argues that the rejection is based on personal knowledge of the examiner, i.e. that the wash step in Dower is only inherent to the "particular application of the general method", and that the only flow cytometric process not requiring a wash step mentioned by the examiner is Applicant's invention which may not be used as a reference. This argument has been fully considered but not deemed persuasive. The instant claims do not exclude a wash step. And, as set forth above, there is no indication that a wash step would negate analysis in real-time as Appellant appears to suggest especially given the fact that Dower does perform real-time analysis, i.e. Dower teaches analyzing with flow cytometery in real time, i.e. the disassociation

of the ligand and the receptor is happening as they are being analyzed in the flow cytometer. Appellant has done essentially the same thing. The basis of the rejection and subsequent arguments has nothing to do with a wash step. The claims require nothing regarding a wash step. The rejection is also not based on Appellant's disclosure. Importantly, Appellant's do not challenge the examiner's assertion that "If one were using the method of Dower to analyze the interaction between a receptor and it's known ligand, as [Applicant] points out, then a wash step would *obviously* not be required" [emphasis added], see page 9 of the brief. Thus, the examiner maintains that the ability of a flow cytometric measurement to discriminate free and bound ligand with-out a wash step was widely appreciated at the time of filing of the instant Application. Appellant's have not asserted that the elimination of a wash step would not be obvious to one of ordinary skill in the art when analyzing the interaction between a receptor and it's known ligand. Again, Appellant has not argued the validity of the examiner's position, only that the examiner has not provided a specific reference for a concept that the examiner believes was widely appreciated in the art. For the purposes of the instant claims, however, any discussion of a wash step appears to be moot given the open language of the claimed invention.

Appellant essentially repeats arguments made at page 10 of the brief regarding the interpretation of the teaching of Baumbach (mistakenly referred to as Dower at page 17 of the Brief and page 4 of the Final action). These arguments have been thoroughly addressed above. The request for an affidavit is improper because Appellant does not appear to directly challenge the validity of any of the assertions the examiner has made, MPEP 2144.03(c).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Examiner
Art Unit 1646

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December 26, 2003

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